UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,113	04/09/2001	William Edward Evans	44158/209598 (5853-3)	2302

29312 7590 10/15/2004

ALSTON AND BIRD LLP
ST. JUDE CHILDREN'S RESEARCH HOSPITAL
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/829,113
Filing Date: April 09, 2001
Appellant(s): EVANS ET AL.

Eric J. Kron
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 24, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-18, 21 and 22 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Li et al. "Allele specific, inverse PCR amplification for genotyping MN Blood group" Biotechniques, vol. 25, no. 3 (1998), pp.358, 360, 361.

Patel et al. "Direct haplotype determination by double ARMS: specificity, sensitivity and genetic applications" Nucleic Acids Research, vol. 19 (1991), pp.3561-3567.

Michalatos-Beloin et al. "Molecular haplotyping of genetic markers 10kb apart by allele specific long range PCR" Nucleic Acids Research, vol. 24 (1996), pp. 4841-4843.

Krynetski et al. "A single point mutation leading to loss of catalytic activity in human thiopurine S-methyltransferase" Proceedings of the National Academy of Sciences USA, vol. 92 (1995), pp. 949-953.

Martin et al. "SNPing away at complex diseases: analysis of single nucleotide polymorphisms around APOE in Alzheimer disease" American Journal of Human Genetics, vol. 67 (2000), pp. 383-394.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) and further in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843).

Li teaches a method of determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism and a second nucleotide polymorphism (see page 360, figure 1) comprising:

(a) obtaining a DNA sample from a human source comprising said contiguous DNA segment (page 358, column 1),

(b) using said DNA sample as a template for polymerase chain reaction amplification of a DNA fragment to form a product which is capable of being subject to intramolecular ligation (page 358, column 2, subheadings "GPA-specific PCR" and page 360, figure 1),

wherein the PCR amplification is performed with

(i) a first primer capable of annealing to a region adjacent to the first NP and distal to the second NPs (see figure 1, where the MN-FP primer is adjacent to the 5'G/T polymorphism and distal from the 3' G/T, C/A/G and C/T polymorphisms)

(ii) a second primer capable of annealing to a region adjacent to the second NP and distal to the first NP (see figure 1, where the MN-CR primer is adjacent to the 3' G/T, C/A/G and C/T polymorphisms and distal from the 5' G/T polymorphism),

(c) ligating the ends of the DNA fragment to each other so as to produce a circular DNA molecule (page 358, subheading "ligation of the amplified fragment" and page 360, figure 1), wherein the ligation brings the first and second polymorphisms into closer proximity on the circular DNA molecule (see figure 1, page 360 and page 361, column 1, which states "ASIP rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR"),

(d) determining the haplotype of the first and second nucleotide polymorphism by allele specific inverse PCR amplification (page 358, subheading "Allele specific PCR" and page 360, figure 1).

With regard to claims 5-8, Li teaches first, second and third NPs that are single nucleotide substitutions with some NPs located between the end NPs whose haplotype is determined (see figure 1, page 360).

With regard to claim 9, Li teaches use of human sources (see page 358, column 1).

With regard to claim 13, Li teaches that the primers are allele specific (see page 360, figure 1).

With regard to claims 14-16, Li teaches determination of each allele of the clinically relevant Glycophorin gene (see page 358, column 1 and page 360, figure 1).

With regard to claims 21 and 22, Li teaches a DNA sequence immediately adjacent to the 5' and 3' NPs which is less than 50 bases long.

Li suggests the use of the method on haplotyping distances that are too long to be PCR amplified (see page 361, column 1).

While Li suggests applying the method to situations with polymorphisms that are distant from one another, Li does not exemplify application of the method to sequences which are 200 to 30,000 bases apart nor the use of long range PCR.

Regarding claim 1 and dependent claims 2-4, Patel teaches that inverse PCR methods such as those used by Li can be applied to haplotype sequences up to 10 kb apart and suggests that even larger regions can be used (page 3567, column 1, lines 6-9).

Regarding claims 11 and 12, Patel teaches restriction digestion to enhance inverse PCR and detection with such digestion (see page 3562, column 1 and page 3563, figure 2)

Patel teaches mutations which are substitutions of single nucleotides and where there are a series of nucleotide polymorphisms located between the two amplified polymorphisms (see page 3561, column 2 and page 3562, figure 1). Patel teaches determining the presence of multiple different polymorphisms (see page 3565, column 1, subheading "Double ARMS Inverse PCR (DARMSI-PCR)". Patel teaches amplification and detection of each haplotype in the same gene, the globin cluster (page 3562, figure 1). Patel further teaches that the method can be used for diagnostic purposes (see page 3567, column 1).

Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long range PCR (page 4842, figures 2 and 3). Michalatos-Beloin also teaches that amplification of up to 40 kb should be possible (see page 4843 (listed as page 4867), column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to amplify the sample of Li since Michalatos-Beloin states "The allele-specific long range PCR products were used as templates for amplification of the STR (page 4867, column 1)". An ordinary practitioner would have been motivated to use long range PCR to prepare the template for the method of Li in order to extend the range of detection of polymorphisms in order to solve the problem of Li that there are "polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1)." Li recognizes the problem in that some haplotypes are too distant to be amplified by standard PCR. Michalatos-Beloin solves the problem using long range PCR. Further, Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). Thus, application of the method of Michalatos-Beloin to the inverse PCR method of Li can be used to increase the accuracy of the Li method. Further motivation to apply the Michalatos-Beloin method to Li is provided by Patel, who teaches that haplotyping using inverse PCR is desirable on long segments, even haplotypes separated by more than 10,000 nucleotides (see page 3567, column 1). This represents further motivation to apply the

method of Li to more widely separated polymorphisms, as well as teachings on how to perform that method.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptopurine (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic

dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are TPMT deficient prior to toxic treatment.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Martin et al (Am. J. Hum. Genet. (2000) 67:383-394).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the listed genes.

Martin teaches haplotype analysis of the ApoE gene in order to analyze the presence of Alzheimer's disease (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the ApoE gene since Martini teaches "Haplotype analysis using family data increased significance over that see in single-locus tests for some of the markers, and for these

data, improved localization of the gene (abstract)." Thus, an ordinary practitioner would have been motivated to haplotype the ApoE gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are at risk for Alzheimer's disease.

(11) Response to Argument

Introduction

This invention is a form of ASIP (allele specific, inverse PCR), in which the only difference from the standard ASIP method is the distance between the first and second nucleotide polymorphisms. To step back, a haplotype is simply the identity of two different nucleotides that are usually nonadjacent to one another, which are polymorphic, on a target DNA strand. So if the first position in the nucleic acid sequence can be A or T and the second position can be A or G, one haplotype could have an A at the first position and an A at the second position while a different haplotype would have an A at the first position and a G at the second position. One method to determine such haplotypes is taught by Li as the ASIP method. ASIP is a method in which a gene is amplified by the polymerase chain reaction method. The amplified gene is then subjected to a self ligation event, in which the two ends of the PCR product are ligated to form a circle. Finally, a second PCR using internal primers is used to amplify the regions between the two ends. Claims 1 and 20 (the independent

claims) are identical to the ASIP method taught by Li, except for the requirement that the nucleotide polymorphisms are separated by less than the required 200 nucleotides.

The DARMSI-PCR method of Patel is very similar to ASIP, but chooses primers to permit restriction digestion between the amplified fragments, so that the primers are not distal to the polymorphisms as required by claim 1.

This difference brings up an important point regarding the grouping of the claims. While Applicant would group the claims based upon the rejections and based upon an argued difference for claims 12 and 22, Applicants arguments focus on the question of what length between the two nucleotide polymorphisms is unobvious. One real difference is the point at which the claims require long range PCR as taught by the secondary references of Michalatos-Beloin and Patel, rather than the regular PCR taught by Li. Long range PCR typically is 10,000 or more nucleotides in length. Therefore claims 1 and 2 and their dependent claims might be differentiated from claims 3 and 4 based upon whether long range PCR is even required by the claim. In claims 1 and 2, Li would be directly applicable without modification other than the use of a different set of primers (though not anticipatory) to any prior art known template where the polymorphisms happen to be separated by 200 to 1000 nucleotides. It is only where the polymorphisms happen to be separated by lengths of 10,000 or more that long range PCR is required, as in claims 3 and 4.

Issue with regard to Rejection of claims 1-16, 21 and 22

Is it prima facie obvious to apply the ASIP method of Li to DNA templates where the polymorphisms are spaced more than the exemplified 30 nucleotide separation of Li?

Do the secondary references of Patel and Michalatos-Beloin provide additional motivation and additional evidence of a reasonable expectation of success to detect polymorphisms spaced more than 10,000 nucleotides apart?

Graham v. John Deere Inquiries

The rejection provided above addresses this issue by providing detailed factual information regarding the inquiries for prima facie obviousness. As noted in the rejection, Li teaches a method in which the steps are precisely identical to those claimed. This fact is not disputed. The only difference resides in the preamble of the claim, where claim 1 has a requirement that the nucleotide polymorphisms of interest be separated by at least 200 nucleotides.

MPEP 2141 makes clear that in order to render the invention prima facie obvious, the references must suggest the desirability of making the combination. In the current case, Li himself suggests that it is desirable to apply his method to nucleotide polymorphisms which are widely separated. Specifically, Li notes "ASIP rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1)." Li expressly recognizes that the ASIP method can be applied to polymorphisms which are widely separated.

That haplotyping is desirably (and would be expected to succeed) on widely separated polymorphisms is shown by the secondary references of Patel and Michalatos-Beloin. Patel expressly notes that

"Although we have so far applied inverse PCR to relatively small genomic fragments (a 865 bp Sau3A1 fragment for DARMSI-PCR and a 427 bp Sau3AI fragment for the corresponding internal control) others have successfully applied inverse PCR to genomic regions of over 10 kb. Thus, having demonstrated DARMSI-PCR is feasible on relatively small regions, it is to be expected that the method should be applicable to regions as long as those amplified by conventional inverse PCR, ie 10 kb. We are currently investigating the use of DARMSI-PCR on larger genomic regions in the B-globin cluster (see page 3567, column 1)."

This statement by Patel is an express suggestion to apply inverse PCR methods, such as those of Li, to regions of 10 kb or greater, in order to permit determination of the haplotype of the target sequence. Michalatos-Beloin makes the even blunter statement that by using long-range PCR "It should be possible to extend molecular haplotyping to distances up to 40 kb. (see page 4867, column 2)." So all of the prior art references specifically motivate, by express statements, the extension of haplotyping to polymorphisms separated by more than 30 basepairs. Li does not provide specific numbers for the spacing of the polymorphisms, though the length is beyond that of PCR. Patel and Michalatos-Beloin specifically indicate that distances of 10kb to 40kb are desirable and also demonstrate that these amplifications can be performed with a reasonable expectation of success.

Hindsight

If the term "hindsight" means anything in patent law, it must mean that the prior art references did not specifically desire the change which is the crux of the invention. In the current case, when Appellant cries hindsight, the situation is as far removed from hindsight as is possible. The invention is the application of ASIP to polymorphisms spaced more than 200 basepairs apart (and as far as 30,000 basepairs apart). The prior art references are replete with teachings that suggest the desirability of extending the distance of the ASIP method.

(a) Li states that ASIP "can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1).

(b) Patel states that "having demonstrated DARMSI-PCR is feasible on relatively small regions, it is to be expected that the method should be applicable to regions as long as those amplified by conventional inverse PCR, ie 10 kb. We are currently investigating the use of DARMSI-PCR on larger genomic regions in the B-globin cluster (see page 3567, column 1)."

(c) Michalatos-Beloin states "It should be possible to extend molecular haplotyping to distances up to 40 kb. (see page 4867, column 2)."

These specific statements written by the scientists in their prior art publications rebuts the argument that the rejections rely upon hindsight. These rejections are based upon the specific motivation expressed in the prior art.

Proximity of Polymorphisms

This argument relies upon a dissection of the specific polymorphisms used by Li without reviewing either the reference as a whole, or the rejection as a whole. In this argument, Appellant conflates the specific example of Li with the entirety of everything that Li teaches. While Li's example clearly uses polymorphisms which are in close proximity to one another, Li's teaching expressly suggests a broader use for the method. When Li states that "ASIP, rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1), this statement cannot be taken as meaning anything other than bringing the polymorphisms close enough by the ligation of the ends so that they can be analyzed by inverse PCR. So Li expressly suggests the step of bringing polymorphisms in closer proximity with one another by ASIP. Li is clearly intent on providing a general method for haplotype analysis. This is expressly indicated by Li, who states that this can be applied to other polymorphisms at page 53 that are separated by distances too far apart for standard PCR. Even if Li does not exemplify bringing polymorphisms closer together, Li expressly teaches and suggests such a course, and expressly teaches methods to analyze haplotypes whose polymorphisms are too far apart for standard PCR. Since Standard PCR can easily amplify 1000 or more bases, Li is discussing polymorphisms that are at least that distant, and which necessarily meet the limitation argued by Appellant.

Secondary References

When Appellant specifically points out that Patel and Michalatos-Beloin do not anticipate the claims, this argument does not address the prima facie obviousness issue. It is the combination of Li with Patel and Michalatos-Beloin that renders the claimed invention obvious. Whether Patel can benefit from the method of Li is not the question, but rather whether Patel suggests the desirability of modifications that would be applied to the method of Li. Only a single suggestion is required from Patel to enhance the method of Li (with regard to the base claim) and that is to perform the method of Li on polymorphisms which are separated by more than 200 basepairs. Patel, as extensively discussed above, clearly suggests that many sets of polymorphisms (including those exemplified by Patel in figure 3) are separated by more than 200 basepairs, and that it is desirable to haplotype using these polymorphisms. This is the motivation which Patel provides the reader of the Li reference which helps render the claimed invention prima facie obvious.

The argument that Michalatos-Beloin teaches away is also incorrect. As MPEP 2123 notes "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." MPEP 2123 also notes "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." So in this case, when Michalatos-Beloin teaches a method which does not require circularization, this does not teach away from the method of Li. The broader disclosure of Michalatos-Beloin suggests that long-range PCR could be applied to haplotyping.

This suggestion of long range PCR, used in the method of Li, for the reasons given by Li that "ASIP, rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1)" will result in the claimed invention, rendering the claimed invention prima facie obvious.

Declaration

The declaration was fully addressed in the final rejection, and reference to that analysis is made here. The Declaration reiterates the position of the inventors that in their scientific opinion the invention would not have been obvious (see, e.g., paragraph 14 of the declaration). While this opinion is given some weight, the ultimate determination of the legal conclusion of prima facie obviousness belongs to the BPAI, based upon the BPAI's analysis of the cited references and motivations derived from those references. It is the considered opinion of the examiner, for the reasons given above and in the final rejection, that the arguments in the inventors own declaration are not persuasive.

Claims 12, 17, 18 and 22

Appellant then separately argues several of the claims. Appellant argues that there is no cited reference showing cleavage of the circularized segment by restriction analysis. Appellant is referred to figure 7 of Patel, which expressly shows relinearization using a restriction enzyme, followed by electrophoresis of the amplified product.

Appellant then argues no motivation to apply the method to the TPMT gene of claim 17 or the APOE gene of claim 18. In fact, specific motivation is given in the rejections. For the TPMT gene, Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". So haplotyping this gene would permit prevention of toxicity using mercaptopurine, a strong motivation to analyze this gene with the method of Li in view of Patel and Michalatos-Beloin. Similar motivation is found in the rejection for the APOE gene as discussed above.

Appellant argues that the selection of specific lengths of the sequences adjacent to the polymorphisms is not taught by the prior art. As noted in the rejection, Li teaches a DNA sequence immediately adjacent to the 5' and 3' NPs which is less than 50 bases long.

Conclusion

The evidence above demonstrates that the combination of Li, Patel and Michalatos-Beloin satisfies the Graham v. John Deere inquiries, including the further requirements of motivation and reasonable expectation of success, rendering the claims prima facie obvious over the cited prior art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Jeffrey Fredman
Primary Examiner
Generalist Level Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
10/5/04

October 5, 2004

Conferees

Gary Benzion, SPE 1637

Jeffrey Siew, SPE 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
10/5/04

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

GARY BENZION
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Full / Partial Signatory Review Sheet

Examiner Name:

Art Unit

Examining Hours:	764
Production:	102
Total Actions:	136
Signed Actions:	112
Allowances:	2
Workflow:	OK
Period Under Review:	
PEFs permitted:	7
ATs permitted:	6
PDs permitted:	1

Cases under Review:

Home SPE's comments are in italics. Reviewer's comments are in regular type

Application 1.	Serial No.: 09/701205 Final
Nelson: PD – AT – PEF – 1 Status=	**PEF1a. CHECKING APPLICATIONS FOR FORMAL MATTERS** The claim amendments filed 2/23/04 are in improper format. Canceled claims should not recite the text of the claim, only the claim number. Examiner should have sent a 30-day letter to have applicant correct this. •
Le Panel	**PEF** • CHECKING APPLICATIONS FOR FORMAL MATTERS The objection of claims 13 and 14 as being improper dependent claims is improper. The examiner states that claim 7 recites that "the HIP apoptosis modulating protein is a HD-interacting polypeptide wherein said polypeptide consists of a sequence...". In fact, the claim recites the opposite. claim 7, line 4+ recites "the HD-interacting polypeptide is an HIP-apoptosis modulating protein and wherein the polypeptide consists of a sequence...". Claims 13 and 14 further limit the HIP-apoptosis modulating protein to which the term "consisting of" in claim 7 does not apply. • The examiner's analysis is correct, however the claim 7 is not structured as described by the examiner in the objection.

Application 2.	Serial No.:10/120,974 non-Final
Brumback: Panel	**AT** • b. WERE ANY UNREASONABLE REJECTIONS MADE The 102 rejection over Murayama et al. and the corresponding 103 rejection are in error (see below). The rejection of claims 1, 4-7, and 13 as anticipated by Murayama is in error because